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Review Article

Effects of noxious stimulation on the electroencephalogram during general anaesthesia: a narrative review and approach to analgesic titration

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Summary

Electroencephalographic (EEG) activity is used to monitor the neurophysiology of the brain, which is a target organ of general anaesthesia. Besides its use in evaluating hypnotic states, neurophysiologic reactions to noxious stimulation can also be observed in the EEG. Recognising and understanding these responses could help optimise intraoperative analgesic management. This review describes three types of changes in the EEG induced by noxious stimulation when the patient is under general anaesthesia: (1) *beta arousal*, (2) (paradoxical) *delta arousal*, and (3) *alpha dropout*. Beta arousal is an increase in EEG power in the beta-frequency band (12–25 Hz) in response to noxious stimulation, especially at lower doses of anaesthesia drugs in the absence of opioids. It is usually indicative of a cortical depolarisation and increased cortical activity. At higher concentrations of anaesthetic drug, and with insufficient opioids, delta arousal (increased power in the delta band [0.5–4 Hz]) and alpha dropout (decreased alpha power [8–12 Hz]) are associated with noxious stimuli. The mechanisms of delta arousal are not well understood, but the midbrain reticular formation seems to play a role. Alpha dropout may indicate a return of thalamocortical communication, from an idling mode to an operational mode. Each of these EEG changes reflect an incomplete modulation of pain signals and can be mitigated by administration of opioid or the use of regional anaesthesia techniques. Future studies should evaluate whether titrating analgesic drugs in response to these EEG signals reduces postoperative pain and influences other postoperative outcomes, including the potential development of chronic pain.

Keywords: analgesia; arousal; electroencephalogram; general anaesthesia; monitor; noxious stimulation

Editor's key points

- Processed electroencephalogram (EEG) monitoring is commonly used to monitor hypnotic state and titrate hypnotic agent administration.
- Understanding and identifying the EEG changes associated with noxious stimulation could lead to better intraoperative antinociceptive/analgesic agent titration.
- Nociception-induced changes in the EEG include *beta arousal*, *delta arousal*, and *alpha dropout* patterns.
- This review focuses on the above EEG patterns, and discusses potential implications for analgesia management and insights for future research.

Noxious stimulation influences the EEG

It is expected that patients undergoing surgery with general anaesthesia should neither experience nor remember the

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procedure.[1] Furthermore, patients should endure as little pain as possible through adequate analgesic treatment throughout the surgical intervention. A major challenge in clinical anaesthesia care is the attenuation of the patients' intraoperative responses to a noxious stimulus. Traditionally, the analgesic component of anaesthesia is predominantly titrated to cardiovascular variables, and most commercially available devices quantify autonomic responses (described in the next section). However, it is important to acknowledge that nociceptive responses can have many dimensions: (1) *somatic responses* (spinal reflexes causing limb movement); (2) *autonomic responses* (brain stem and hypothalamic effects causing changes in heart rate, ventilatory frequency, vasoconstriction, and pupillary changes); (3) *cognitive arousal and memory formation* (subcortical and midbrain structures causing general arousal, mediated via the forebrain and cortex for attention and memory); and (4) various endocrine, coagulation, and immune-inflammatory responses. The clinical significance of the neurophysiologic responses (as measured by frontal EEG electrodes) to noxious stimulation is less clear. These responses are more transient and may or may not occur concurrently with autonomic reactions. However, they are clear indications that anaesthesia has, in some way, failed to fully suppress the brain's response to surgery-induced tissue damage. The degree to which this situation influences long-term patient outcomes is unknown at present.

The focus of this narrative review article is to describe the particular effects of noxious stimulation on (frontal) EEG recordings, and the possible underlying changes in neurophysiological activity. The EEG response can take on at least three very different patterns. At lower doses of anaesthesia (e.g. for maintenance with volatile anaesthetics in the absence of opioids, typically 0.5–1.0 MAC effect site concentration) the (frontal) EEG can react with stronger oscillations in the beta (12–25 Hz) range. This is called *beta arousal,* and it often occurs together with somatic movement as a reaction to a painful stimulus. Other reactions, predominately at higher administered doses of anaesthesia medications or during balanced anaesthesia (analgesics plus anaesthetics), are *delta arousal* and *alpha dropout*. Delta arousal is an increase in slow frequencies (0.5–4 Hz), and alpha dropout is a decrease in EEG alpha power (8–12 Hz).

Although these EEG responses appear to be neurophysiologic biomarkers of nociception, it remains to be seen whether adequate analgesic administration will consistently prevent their occurrence and improve clinical outcomes. Intraoperative consideration of EEG biomarkers representative of intense periods of noxious stimulation is a paradigm shift not easily reviewed via systematic, automated search strategies. We approached the subject by expanding on previous knowledge and using references found in key papers. Because we focused on the description of EEG patterns that occur perioperatively as a response to noxious stimulation we tried to group the relevant literature into the (1) reaction of processed EEG indices, (2) reaction of the raw EEG, and (3) findings from animal models.

Current state of analgesia monitoring in the operating theatre

Using EEG-derived information from a patient undergoing surgery is becoming more and more common to help navigate general anaesthesia. With some exceptions, available EEG-based monitors focus on the *hypnotic component* of anaesthesia. This is done by tracking the changes from low-amplitude, high-frequency activity during wakefulness to high amplitude, low frequency activity during anaesthesia levels adequate to perform surgery.[2] The most widely used indices are the Patient State Index (PSI™; Sedline, Masimo, Irvine, CA, USA),[3] the bispectral index (BIS; Medtronic, Dublin, Ireland),[4] and the state and response entropy (SE/RE; GE Healthcare, Helsinki, Finland).[5] By design, these monitoring systems do not explicitly focus on EEG changes caused by noxious stimulation. Because these systems are designed to measure the relative high frequency EEG power, they are reasonably sensitive in detecting beta arousal after noxious stimuli, but less sensitive for detecting the changes in lower frequency activity that can occur with stimulation (e.g. delta arousal or an alpha dropout).

Studies using processed EEG indices are summarised in Table 1. Previous research with the BIS demonstrated a failure to detect noxious stimuli during volatile anaesthesia, whereas a specific focus on EEG alpha band features was successful.[24] The challenge for developing a more holistic EEG-based monitoring system is to include algorithms that can detect all the different patterns of EEG changes induced by noxious stimulation. Most commercially available pain monitoring systems do not use EEG parameters. Instead, they include heart rate variability,[25] modelled drug and opioid concentrations,[26] the polysynaptic spinal withdrawal reflex,[27] plethysmographic pulse wave amplitude, and the heartbeat interval,[28] or a multivariate model from ECG, BIS, blood pressure and other factors.[29] Recently the nociception level (NoL) index has been developed which amalgamates several different dimensions of autonomic function, and was shown to improve intraoperative analgesic titration and cardiovascular stability.[30,31]

The minority of EEG-based monitoring systems that explicitly aim at evaluating the analgesic component are: the Brain Anaesthesia Response monitor (BAR; Cortical Dynamics Ltd, North Perth, Australia),[7,32] the composite variability index (CVI) from the bispectral index (Medtronic),[9,33,34] and the qNOX (Qantium Medical, Barcelona, Spain), which uses the ratios between the energies of the EEG signal in different frequency ranges to track noxious stimulation.[8] It was calibrated to nail-bed pressure as a noxious stimulus,[8] but seems to work for stimuli such as laryngeal mask airway insertion,[6] a stimulus known to also trigger beta arousal. Hence, it may be comparable with the response entropy index.[10,11,16] The BAR, based on neural field modelling, uses autoregressive and moving averages to estimate separate *hypnotic* and *analgesic* components.[7,32] If we are to design a holistic EEG monitoring system, we have to understand all the different responses triggered by noxious stimuli, and then implement tools that can detect them. A thorough monitoring of the raw EEG or the density spectral array (DSA) regarding the possible types of reaction to a noxious stimulation adds no more costs or risks to the patient because the EEG information is available and should be used for intraoperative decision-making anyway.[35] It can help the anaesthesiologist to identify and react to the different reaction types by adjusting analgesia, hypnosis, or both, as it can help the scientific community further understand the situations the different reactions occur. Therefore the EEG-based approach to monitor reactions to noxious stimulation may provide a relevant addition to anaesthesia monitoring as it positively answers the questions that are relevant to a useful application.[36]

Table 1 Studies investigating the influence of noxious stimulation on the processed EEG. BAR, brain anaesthesia response; BIS, bispectral index; CI, cortical input; LMA, laryngeal mask airway; LOC, loss of consciousness; n.d., not described; NMB, neuromuscular block; RE, response entropy; SE, state entropy; SEF, spectral edge frequency.

Author	Sample size	Group	M/F	Drugs	EEG	Stimulus	Finding/effect on EEG
Melia and colleagues[6]	140 patients (77 with noxious events)	1	68/72	Propofol/remifentanil	Frontal qCON	Laryngeal mask insertion	51 non-responders, 26 responders (movement to stimulus) higher qCON in responders
Shoushtarian and colleagues[7]	25 patients (20 used)	2	19/1	Propofol (BIS: 40–60); fentanyl total dose: 12 μg kg^{-1} (moderate dose group); 24 μg kg^{-1} (high dose group)	Frontal BIS/BAR	Skin incision/ intubation/ sternotomy	CI shows different reactions to noxious stimulation at different doses of fentanyl
Jensen and colleagues[8]	60 patients	1	n.d.	Propofol/remifentanil	Frontal with qCON	Suture, laryngoscopy, LMA, tracheal intubation, surgical incision	Higher qCON and qNOX in movers (n=20), indicative of beta arousal
Sahinovic and colleagues[9]	120 patients	12		Propofol to BIS 30, 50, 70/ remifentanil 0, 2, 4, 6 ng ml^{-1}	Frontal with BIS	Electrical tetanic, ulnar nerve	Beta arousal (higher BIS in responders)
Guerrero and colleagues[10]	20 patients	1	8/12	Sevoflurane, 3% and 4% end-tidal concentration	BIS/Entropy	Electrical tetanic	Only significant increase in RE (beta arousal)/motor response
Musialowicz and colleagues[11]	32 patients	1	28/5	Propofol, 2–8 mg kg^{-1} h^{-1} to BIS <60/sufentanil 2–8 μg kg^{-1} h^{-1}/ 0.1 (+0.02) mg kg^{-1} pancuronium	Frontal with BIS + entropy sensor	Intubation, skin incision, sternotomy	Beta arousal (BIS, EMG, and RE–SE increase)
Aho and colleagues[12]	38 patients	2	0/38	Propofol 1 mg kg^{-1} (ind)/ sevoflurane 8% + N_2O 67%/ rocuronium 0.6 mg kg^{-1} (1 grp)	Frontal with entropy sensor	Skin incision	In 15/15:(total: 30) beta arousal; SE and RE increase
Doufas and colleagues[13]	24 volunteers	1	n.d.	Sevoflurane induction 6–8%/ desflurane (maint) 4–5%/saline, succinylcholine (1 mg kg^{-1}), mivacurium (0.15 mg kg^{-1})	Frontal with BIS	Electrical stimulation, anterior thigh	Beta arousal (higher BIS)
von Dincklage and colleagues[14]	12 volunteers	1	12/0	Propofol (increase in 1 μg ml^{-1} steps until no reaction to stimuli or 7 μg ml^{-1})	Frontal with BIS	Electrocutaneous stimuli, ipsilateral sural nerve	Beta arousal (higher BIS) when reaction to stimuli
Sandin and colleagues[15]	10 volunteers		6/4	Sevoflurane 8% (2 min) then 4%, then targeted to 1, 1.5, and 2 MAC	Frontal with BIS	Transcutaneous electrical nerve stimulation/ice water pain test	Beta arousal (higher BIS) only observed at 1 MAC
Weil and colleagues[16]	105 patients	2	44/61	Propofol 4–5 μg ml^{-1} (higher if no LOC)/remifentanil (intub) 2, 4, 6, or 8 ng ml^{-1}/atracurium 0.5 mg kg^{-1} or cisatracurium 0.2 mg kg^{-1} in NMB group	Frontal with entropy sensor	Intubation/incision	Beta arousal (higher RE, SE, RE –SE) after intubation in movers
Ekman and colleagues[17]	25 patients	2	8/17	Sevoflurane 8% (2 min), 4% (3 min)/rocoronium to 50%, 95% depression	Frontal with BIS	Electrical tetanic, ulnar nerve	Beta arousal (higher BIS, dependent on NMB)
Ekman and colleagues[18]	13 patients	1	4/9	Sevoflurane (induct: 2 min @ 8%; 10–15 min @ 4%) after baseline recording: 0.6 mg ml^{-1} rocuronium	Frontal with BIS	Electrical tetanic, ulnar nerve	Beta arousal (higher BIS), that was stronger in absence of NMB. With block, no increase in 36 –47 Hz power and no decrease in 36–47 coherence
Morimoto and colleagues[19]	18 patients	2	11/7	Induction: thiopental 3 mg kg^{-1} and 5% sevoflurane;	Frontal with BIS	Intra-abdominal irrigation	

Continued

Table 1 Continued

Author	Sample size	Group	M/F	Drugs	EEG	Stimulus	Finding/effect on EEG
				maintenance: sevoflurane and nitrous			Decrease in BIS and SEF95 that could be prevented with fentanyl (delta arousal)
Menigaux and colleagues[20]	50 patients	2	33/17	Propofol (effect site conc. 4 μg ml^{-1})/vecuronium 0.1 mg kg^{-1}/esmolol (bolus 1 mg kg^{-1}, then infusion of 250 μg kg^{-1} min^{-1})	Frontal with BIS	Intubation	Beta arousal (higher BIS), blunted by esmolol
Guignard and colleagues[21]	50 patients	5	26/24	Propofol (effect site conc. 4 μg ml^{-1})/remifentanil (0, 2, 4, 8, or 16 ng ml^{-1})	Frontal with BIS	Laryngoscopy, intubation.	Beta arousal (higher BIS), concentration dependent effect of blunting the increase by remifentanil
Coste and colleagues[22]	30 patients	2	20/10	Propofol (effect site conc. 4 μg ml^{-1})/remifentanil (4 ng ml^{-1}) and either 50% air in oxygen (control) or 60–70% N_2O in oxygen	Frontal with BIS	Orotracheal intubation	Beta arousal (higher BIS) after intubation; movers were only observed in control (no N_2O) group
Iselin-Chaves and colleagues[23]	40 patients	3	23/17	Propofol in steps 1, 2, 4, and 6 μg ml^{-1}/alfentanil (either 0, 50, 100 ng ml^{-1})	Frontal with BIS	Spring-loaded rod to apply periosteal pressure to the tibia	Beta arousal (higher BIS),

EEG responses to general anaesthesia and to surgical stimulation

As is comprehensively described elsewhere,[37,38] sufficient concentrations of propofol or an inhalation ether change the patient's EEG from a low-amplitude, high-frequency pattern (the so-called 'desynchronised' EEG) to one that looks similar to that of slow wave sleep and some comas[2] – namely, a high-amplitude, slower-frequency pattern, with dominant EEG activity in the delta and alpha ranges.[39] We have to recognise that these transitions are non-linear.[40] For example, during anaesthesia induction, episodes of paradoxical excitation (beta range) of the frontal EEG beta range may be observed.[2,41] Similarly, at excessively high doses of anaesthetic medication the EEG does not result in higher and higher amplitudes but eventually decreases in amplitude and finally becomes discontinuous. Low EEG amplitude at both ends of the dose relationship is another example as to how representing surgical anaesthesia on a single axis numeric scale is a gross oversimplification. Many anaesthesiologists use a multidimensional mental model for different clinical goals; for example, although unconsciousness and analgesia may be synergistic, the pain/analgesia axis can often be considered independently of the arousal/hypnosis axis (Fig. 1) for pharmacologic decision-making (i.e. does this patient need more disruption of cortical processing or more analgesia?). It is also being increasingly realised that a variety of other factors such as age, patient cognition, and co-morbidities can influence intraoperative EEG patterns.[42–45]

It might be assumed that surgical stimulation acts to 'wake the patient up' by overwhelming the pharmacodynamic effects of hypnotic drugs and causing premature arousal, which would result in EEG features towards those relating to consciousness (lower amplitude EEG, less delta waves, more beta waves). However, noxious stimulation under general anaesthesia can also trigger atypical changes in the EEG that do not follow this classical arousal pattern. In the following sections we describe the proposed mechanisms of the different responses to noxious stimulation. We show three tables to summarise the work that has been done on this subject. Tables 1 and 2 present results from studies that deal with the EEG reaction to noxious stimuli in patients or volunteers by either describing changes in the processed EEG (Table 1) or in the raw EEG (Table 2). Furthermore, Table 3 contains information from studies conducted with animal models.

Beta arousal

The observation of an acceleration in the EEG after painful stimulation (beta arousal) was described in the very earliest days of EEG clinical research.[62]

Mechanisms of beta arousal

Although it is difficult to draw definitive conclusions regarding the underlying neurobiology that triggers these changes in the EEG during surgical anaesthesia, there is evidence that points toward an increase in cortical activity – and the concomitant increase in beta wave EEG power – that marks progression towards either a dream-like state or wakefulness.[63,64] The neuroanatomy and neurophysiology of the beta arousal response are quite well understood. In 1949, Moruzzi and Magoun[65] demonstrated that beta arousal could be replicated by electrical stimulation of the ascending reticular activating

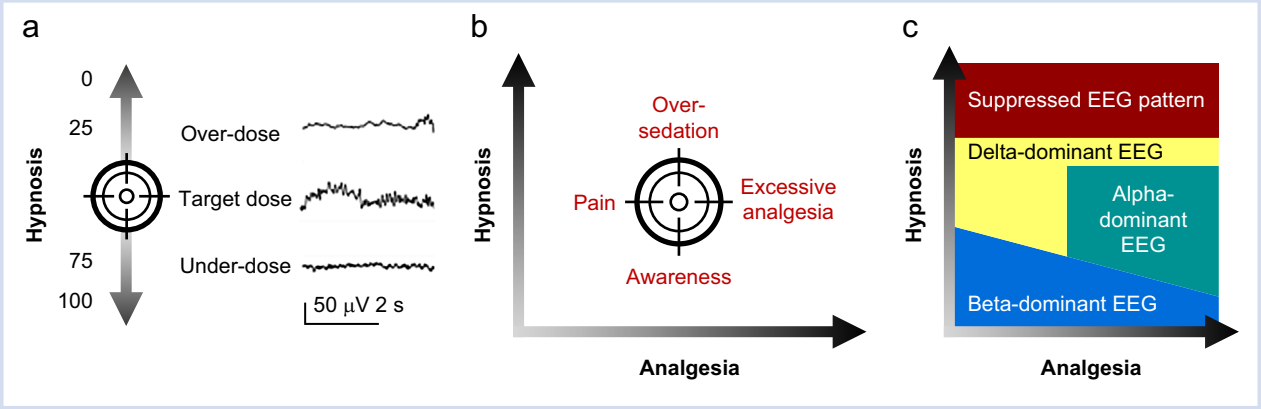

Fig 1. Schematic concept of hypnotic and analgesic drug titration. (a) Relation between calculated index values of processed electroencephalographic (EEG) monitors and the exemplary EEG traces for the different states. (b) The desired target range of general anaesthesia should prevent the patient from awareness (hypnotic management) and pain (analgesic management) without overdosing. (c) Different main classes of typical EEG patterns as induced by different doses of the hypnotic and analgesic drugs.

system that regulates transitions between sleep and wakefulness. Since then, a large literature has burgeoned, showing in some detail, that noxious stimulation acts to increase aminergic[66] and cholinergic[67] neuromodulators in the brain stem to *de*polarise the thalamus and thus inhibit the *hyper*-polarisation-dependent slow wave thalamocortical oscillations in the EEG.[2,68] Aminergic systems are important mediators of beta arousal in the EEG.[69] Clinical studies have shown that a beta-adrenergic receptor blockade helps to block arousal reactions after the stimulus of tracheal intubation.[20,70] Taylor and colleagues[71] elegantly demonstrated that dopaminergic systems in subcortical areas also seem to play an important role in beta arousal and reversal of hypnosis. However, a beta arousal reaction seems to occur only if the cortex is in a state that is receptive to noxious stimulation, when the patient is under a low doses of anaesthesia in combination with insufficient analgesia.[53,72,73]

As shown in Tables 1 and 2, early in the course of general anaesthesia this arousal reaction is commonly associated with the stimuli of laryngoscopy or the initial incision.[47–49] At the other end of the operation, noxious stimulation in the early postoperative period may accelerate arousal during emergence. Analgesic treatment with epidural lidocaine delayed features of arousal.[74] Fig. 2a displays a schematic of a beta arousal. Noxious stimulation can alter the required doses of the anaesthetic to maintain adequate hypnosis. Work by Röpcke and colleagues[50] for instance illustrates the influence of noxious stimuli on patients' desflurane requirements. Systematic quantification of concentration–effect curves revealed an additional 2% desflurane was required for equivalent sigmoid dose–response relationships in the presence of surgical stimulation, as compared with the state without noxious stimulation. This implies that we can expect to see a beta-arousal response to surgery mainly at low concentrations of hypnotics, and when used without adjunctive opioids.

The clinical message would appear to be simple: 'Give enough hypnotic drug to prevent beta arousal in the face of the ongoing level of stimulation'. However, as always in biology, the situation is more complex. Intraoperatively, at seemingly adequate levels of general anaesthesia, arousal reactions in the EEG that are different from beta arousal are common. In one of the first papers in this field, Kochs and colleagues[54] presented results indicating that noxious stimuli during surgery can increase EEG delta power and decrease EEG alpha power, a reaction that stands in complete contrast to the change towards higher EEG frequency activity seen when the patient emerges at the end of anaesthesia. The authors concluded that ' … *the mechanisms for arousal during emergence from anaesthesia may be quite different from those for intraoperative arousal induced by noxious stimulation* … '. They loosely termed this phenomenon *paradoxical arousal* or *delta arousal*. An example of this paradoxical arousal, that is an increase in EEG delta power accompanied by the decrease in EEG alpha power, is shown in Fig. 3.

Delta arousal

During modern 'balanced anaesthesia' techniques, typically involving opioids, neuromuscular block, along with propofol anaesthesia, volatile gas anaesthesia, or both, beta arousal is somewhat mitigated because opioids act synergistically with hypnotic drugs to obtund EEG responses to the stimulus.[24] In the previously mentioned work by Kochs and colleagues,[54] patients receiving 66% nitrous oxide were placed into low (0.5 MAC) and high (1.0 MAC) isoflurane groups. EEG delta power increased with incision. The increase was stronger in the low MAC group (+181%; electrode F3) than in the high MAC group (+44%; frontal and occipital electrodes). Alpha power decreased by about half in both groups. The main effect was seen frontally. Although all these patients received nitrous oxide, delta arousal to noxious stimulation can appear in its absence. Hartley and co-workers[46] have shown that even the mild stimulus of intravenous cannulation increased delta waves in children receiving sevoflurane monoanaesthesia. Kiyama and Takeda[75] reported a similar relative increase in delta and loss of alpha EEG power in response to incision, which were completely prevented by pre-existing epidural blockade. More recently these results were replicated[76] in a large group of patients undergoing a more clinically routine fentanyl and desflurane or propofol anaesthesia regimen (aiming for a BIS of 40–55; i.e. the index range recommended to perform surgery). Loss of alpha activity was associated with

Table 2 Studies investigating the influence of noxious stimulation on the raw EEG. BIS, bispectral index; ET, end-tidal; MF, median frequency; NMB, neuromuscular block.

Author	Sample size (patients)	Groups	M/F	Drugs	EEG	Stimulus	Finding/effect on EEG
Hartley and colleagues[46]	51 paediatric	3	26/25	Sevoflurane 2.5% (ET)/ tetracaine 4% (1 grp)	8-channel EEG	'PinPrick', clinical cannulation	Delta arousal in 36% (only without topical anaesthesia)
Ekman and colleagues[18]	13	1	4/9	Sevoflurane (induct: 2 min @ 8%; 10–15 min @ 4%) after baseline recording: 0.6 mg ml^{-1} rocuronium	Frontal with BIS	Electrical tetanic, ulnar nerve	Beta arousal (higher BIS), but NMB BIS response: with block, no increase in 36–47 Hz power and no decrease in 36–47 coherence
Kox and colleagues[47]	42	1	32/10	Sufentanil 0.5 (range, 0.2–0.6 μg kg^{-1}) followed by etomidate 0.3 (range, 0.2–0.8 mg kg^{-1})	19-channel EEG	Intubation	Delta decrease (all electrodes); theta decrease (predom. Central locations); alpha increase (all electrodes); beta increase (all electrodes)
Rundshagen and colleagues[48]	25	1	8/17	Propofol 2 mg kg^{-1}, fentanyl 2 g kg^{-1} (as bolus with individual adaption) + NMB flurane	8-channel EEG	Intubation	alpha and beta arousal; delta decrease
Rundshagen and colleagues[49]	25	1	0/25	Thiopental (5.7 [0.2] mg kg^{-1})/ fentanyl (3.0 [1.3] mg kg^{-1})	19-channel EEG	Intubation	Delta decrease (all electrodes); theta decrease (C3 - Cz, C4 - Cz); alpha increase (all); beta increase (all except central positions)
Hagihira and colleagues[24]	48	4	20/28	Thiopental (3 mg kg^{-1}); isoflurane (1%) or sevoflurane (1.5%)	Frontal with BIS	Incision	Decrease in low (2–6 Hz) and high (7–13 Hz) bicoherence
Röpcke and colleagues[50]	24	2	0/24	Propofol 2.2 mg kg^{-1}, 7 1–1.6 MAC desflurane	Frontal with BIS	Surgical stimulation	Beta arousal (higher BIS, MF, SEF95) up to 8% desflurane
Litscher and Schwarz[51]	25	1	12/13	Fentanyl (0.05–0.1 mg)/ thiopental (3–5 mg kg^{-1}/ vecuronium (0,1 mg kg^{-1}); maint: isoflurane (0.6% ET)/ O_2/N_2O mixture (FiO_2=0.3)	2-channel frontal	Skin incision	0.05–2 Hz decrease; 2–4 Hz increase
Bischoff and colleagues[52]	34	3	0/34	Etomidate 0.3 mg kg^{-1}/ vecuronium 0.1 mg kg^{-1}/ isoflurane 0.6%/N_2O 66%	17-channel EEG	Laparotomy/ mastectomy	Delta (laparotomy), theta (mastectomy) arousal and alpha decrease
Wilder-Smith and colleagues[53]	20s	2	12/8	Propofol 3 mg kg^{-1} or thiopentone 6 mg kg^{-1}; nitrous oxide	4-channel EEG	Laryngoscopy/ intubation	Relative theta to beta power increase and delta decrease, stronger in thiopentone group
Kochs and colleagues[54]	46s	4	21/25	Etomidate 0.3 mg kg^{-1}/ fentanyl 1.5 μg kg^{-1}) vecuronium 0.1 mg kg^{-1} 6% N_2O in O_2 and isoflurane (0.6 –1.2% ET)/vecuronium (2–3 mg)	17-channel EEG	Skin incision and abdominal surgery	Increase in delta power that was stronger at 0.6% isoflurane

Table 3 Studies investigating the influence of noxious stimulation on the raw EEG in the animal models. MF, median frequency; SEF, spectral edge frequency.

Author	Sample size	Drugs	EEG	Stimulus	Finding/effect on EEG
Johnson and colleagues[55]	55 lambs (infant)	Halothane (1.2%)	1-channel EEG	Castration	MF increase; stronger in older lambs
Murrell and colleagues[56]	46 rats	Halothane	4-channel EEG	To tail: mechanical, thermal, electrical	MF increase: overall: electrical; in some areas: thermal; no change: mechanical
Otto[57]	7 dogs	Isoflurane (1.9%)	2-channel EEG	Noxious visceral stimulation	SEF80, MF, alpha power, beta power, alpha/delta ratio and beta/delta ratio increase
Orth and colleagues[58]	16 rats	Halothane/propofol (0.8 and 1.2-fold dose to prevent response to tail clamp)	4-channel	Electric tetanic to tail/tail clamp	Propofol (0.8): EEG activation; propofol (1.2): paradoxic decrease in SEF95; halothane: EEG activation
Murell and colleagues[59]	13 horses/ponies	Thiopental (ind)/ halothane (min. 1.2%)	1-channel EEG	Castration	Amplitude decrease and MF increase
Otto and Mally[60]	25 ewes	Isoflurane (2.2%)	2-channel EEG	Skin incision/ drilling/pin insertion	Decrease and increase in MF and SEF80
Antognini and Carstens[61]	10 goats	Isoflurane (0.6, 0.9, 1.1, and 1.4 MAC)	10 recording sites	Clamp on dew claw	Delta to alpha power decrease for concentrations <1.1 MAC

an increase in delta power in many patients at the initiation of surgical stimulation. These observed delta arousals may be limited to a certain frequency range, because although delta power may increase to a stimulus, the power in the sub-delta range can decrease.[51] This finding may contradict the term 'paradoxical' arousal, because it describes a stimulus-induced shift towards faster frequencies, which does not seem 'paradoxical' at all.

Influence of type of surgery

Although the clinical relevance of the delta arousals remains uncertain, the source of the noxious stimulation has some influence on the type of arousal response. Bischoff and colleagues[52] showed that the delta amplitude increase was more pronounced for laparotomy (body cavity surgery) than mastectomy (body surface surgery). The increase in delta power during laparotomy was most pronounced at frontal (F3) positions with 245%, in contrast to only 45% at occipital positions (O1). Morimoto and colleagues[19] observed a similar profound increase in (frontal) delta waves (see Fig. 2 in their paper) when they reported a decrease in BIS value with abdominal irrigation. This increase in slow waves can be markedly reduced by opioids, but not by increasing concentrations of the inhalation anaesthetic. Other research groups using other indices have also observed this (frontal) decrease in the processed EEG index.[12]

Mechanisms of delta arousal

Delta waves are understood to represent synchronous synaptic input onto cortical cells as occurs during sleep and anaesthesia.[77] This hyperpolarisation can release cortical cells from their sensory input, and when occurring in combination with decreased cortical activation by the ascending reticular activating system, delta waves develop.[68] The link from these findings to the paradoxical response to noxious stimulation is not known, and may be related to specific drugs used and type of stimulation. It would seem that *visceral* pain pathways[19,52] are more likely to stimulate the specific mesencephalic centres that cause cortical delta waves. Using similar techniques to those used by Moruzzi and Magoun,[65] Kaada and colleagues[78] found that high-frequency stimulation of the midbrain reticular formation can induce theta and delta waves in about a third of the experiments.

The addition of nitrous oxide to volatile anaesthetics seems to transiently augment delta power,[79,80] and it is speculated that *N*-methyl-D-aspartate receptor blockade by nitrous oxide has the effect of hyper-synchronising oscillations. Conversely, the co-administration of remifentanil during higher doses of

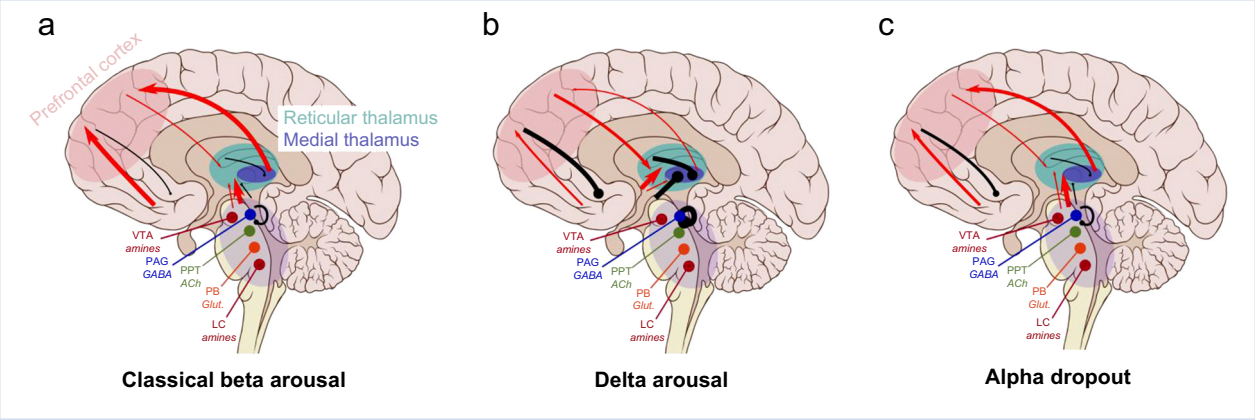

Fig 2. Illustration of proposed alterations in regional neuromodulators and communication, associated with the three patterns of nociceptive arousal. The width of the arrows indicates strength of effect. Red arrows indicate excitation, and black round-heads indicate inhibition. (a) Brain stem activation of both the posterior and anterior arousal pathways resulting in widespread thalamocortical depolarisation – and the resultant beta arousal pattern. (b) Here, we postulate the presence of exaggerated GABAergic negative feedback loops in some of the brain stem and thalamic regions, so that increase noxious stimulation is converted to slow wave activity in the EEG. (c) A similar pattern to the classic beta arousal is shown except that there is sufficient intrinsic inhibitory GABAergic hypnotic drug effects in the cortex (black round-headed arrow), that – although the thalamocortical oscillations have been disrupted – the cortex is itself still relatively hyperpolarised. ACh, acetylcholine; GABA, gamma-aminobutyric acid; Glut, glutamate; LC, locus coeruleus; PAG, periaqueductal grey matter; PB, parabrachial nucleus; PPT, pedunculopontine tegmental nuclei; VTA, ventral tegmental area.

propofol anaesthesia decreases delta power and increases alpha power.[81]

Although originally termed delta arousals,[51,54,73] these delta responses may not necessarily represent progression towards the restoration of consciousness. Neuroanatomical information from the coma and sleep literature provides some insight into the source of these delta power increases. Intermittent rhythmic delta activity is non-specific and seen in various comas of mild severity, but can also occur in normal subjects.[82] In contrast, continuous high-voltage delta activity typically develops with substantial lesions involving tracts carrying subcortical arousal information and can be localised or generalised depending on the extent of the lesion. Although intermittent rhythmic delta activity is associated with mild stimulation in some patients, during natural sleep it is not unusual to see benign and non-specific rhythmic delta activity restricted to frontal leads, typically in lighter stages of sleep.[83] Fig. 2b illustrates the proposed mechanism of delta arousal.

Alpha dropout

The development of a steady-state alpha oscillation during general anaesthesia is primarily driven by hypnotic drugs interacting with underlying patient factors. For volatile anaesthetics, the alpha power is typically maximal in the moderate dose range, with diminished alpha power observed at both lower concentrations (<0.5 MAC) and at higher concentrations (where the EEG might be dominated by delta activity, discontinuities, or both). A sudden episodic loss of frontal alpha power is a relatively common response to noxious stimulation. Opioids can prevent or recover an alpha dropout.[84] These observations have given rise to the concept that (frontal) maximal alpha power is a reasonable biomarker for the titration of intraoperative opioids.[85] Hagihira and colleagues[24] looked at the effect of abdominal surgery in patients anaesthetised with isoflurane or sevoflurane (0.7–0.8 MAC). They gave a bolus of fentanyl either 5 min before incision (looking at EEG at incision and 5 min after) or 5 min after incision (and looked at EEG 5 and 10 min after incision). They observed a decrease in EEG features in the alpha band after incision, which then recovered with subsequent fentanyl administration; in contrast, if fentanyl was given before incision to provide sufficient analgesia, the prominent alpha oscillatory activity did not decrease with incision.[24] Mackay and colleagues[86] looked at pre-*vs* post-stimulus changes in alpha power and burst suppression in response to two stimuli (intubation and incision) with three levels of fentanyl. Loss of alpha power was more pronounced in the low opioid (1 μg kg^{-1}) group. These studies highlight the capability of adequate analgesia management to prevent the stimulus induced decrease in EEG alpha power and hence possibly prevent pain-triggered arousal events.

Mechanisms of alpha dropout

In animals it has been shown that noxious stimuli act to depolarise the thalamus via the effects of ascending aminergic and cholinergic input on the reticular nucleus of the thalamus. EEG alpha rhythms may be associated with the activity of thalamic pacemaker neurones, the intrinsic oscillatory rhythm of neurones in the thalamic relay nuclei, and their interactions with cortical areas.[67] The increase in frontal alpha power and the development of the frontal alpha spectral peak, that is the anteriorisation of alpha power, is a well-observed phenomenon during general anaesthesia.[87] Modelling work relates the high frontal alpha power during propofol to simple, low-dimensional, synchronised oscillations in thalamocortical loops,[88] and hyperpolarised thalamic calcium current-induced bursting activity. Hence, the loss of alpha power induced by a noxious stimulus may reflect increased

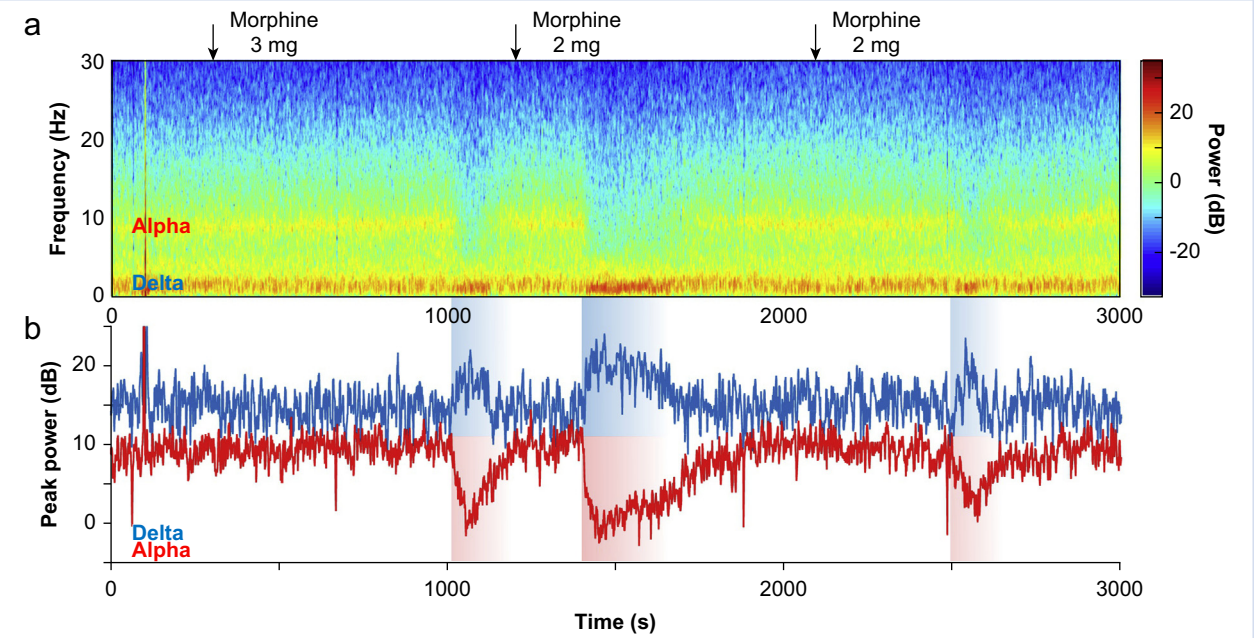

Fig 3. Example of periods of electroencephalographic (EEG) delta arousal and alpha dropout t ~1100, 1500, and 2600 s. (The EEG spectrogram was taken from a patient during a laparotomy under sevoflurane [1.1–1.25 MAC] and increments of morphine 3 mg at 300 s and a further morphine 2 mg at 1200 and 2100 s.) (a) Representation of spectral changes over time shows strong delta (~2 Hz) and alpha (~10 Hz) power during the course of anaesthesia as indicated by the red (delta) and yellow (alpha) horizontal line. At the mentioned time points the red in the delta power becomes more intense (increase in power: delta arousal), and the yellow alpha line shows an interruption with a turn to cooler colours (decrease in power: alpha dropout). (b) In order to elucidate the delta arousal and alpha dropout, the plot presents the peak power in the delta and alpha frequency band over time. At the mentioned time points, delta peak power increases whereas alpha peak power decreases.

complexity of communication between thalamus and cortex, because the depolarised thalamus switches from its hyperpolarised burst-firing mode to a more continuous firing mode. This is manifest as loss of alpha power in the EEG signal, a reaction analogous to a partial beta arousal.

Curiously – as described in the previous section – this can occur in the presence of a strong, or even increased slow oscillation, which is clear evidence that it is possible to achieve cortical, slow, up–down states that are independent of the thalamus. A down state presents a hyperpolarised membrane potential of the neurones and an up state reflects a more depolarised state,[89] that is periods of sustained firing of neurones and quiescent episodes. Because these EEG responses can occur separately, it clearly demonstrates the dependence of alpha oscillations on the thalamus but also the independence of delta oscillations from the thalamus. This alpha dependence on the thalamus manifests itself in a few types of coma that show alpha-dominant rhythms. Examples include those induced by barbiturate or benzodiazepine overdose, some anoxic encephalopathies (typically these cases have a predominance of low alpha activity, 7–8 Hz, and sometimes referred to as alpha–theta coma), and specific sub-tentorial vascular infarcts rostral to the pons that spare the thalamus.[90] Stimulation cannot change these alpha-dominant patterns,[82] suggesting that the thalamus is effectively uncoupled from its depolarising input arising from the pons and other brain stem nuclei. The described mechanisms of alpha dropout are highlighted in Fig. 2c.

Clinical consequences

As a component of anaesthesia monitoring, the changes in the EEG coincident with a noxious stimulus have been hitherto somewhat neglected. A major consideration during anaesthesia care is to suppress the responses to noxious stimulation. Autonomic responses are clearly related to various perioperative cardiovascular complications, but it remains to be determined if pure EEG nociceptive responses have significant long-term clinical consequences.

Nevertheless, the practitioner should be aware of the possibility of a delta arousal as a response to body cavity noxious stimulation, as this phenomenon causes EEG indices to falsely suggest that hypnotic dose is excessive,[19] and hence might trigger an erroneous response on the part of the anaesthesiologist to decrease the hypnotic drugs. Clearly this is potentially a major problem for any putative closed-loop anaesthesia/analgesia drug control device. For this reason, new EEG monitors should be able to quantitatively track the details of the changes in low (delta) and moderate (alpha) frequency power in the spectrogram so the clinician can respond appropriately.

The other immediate consequence of the nociceptive EEG effects is to guide intraoperative opioid titration. A good argument can be made for opioids to be titrated to maximise EEG alpha power – and avoid alpha dropouts – in the face of surgical nociceptive input (see example in Fig. 3). According to recent theories, a maximised alpha power would indicate an

adequate level of anaesthesia, that is a state of idling communication between thalamus and cortex that minimises the reaction to a noxious stimulus. Whether this practice results in improved intraoperative autonomic stability and less postoperative delirium,[91] pain, and immune suppression has yet to be evaluated in large clinical trials.[85] In order to appropriately use EEG alpha power as a potential marker of anaesthesia quality,[92] it is important to personalise the EEG pattern. Some patients with neurodegeneration,[93] previous stroke,[94] or sleep disorders[95] may have less alpha power than expected. Furthermore, patients of older age[43,45,96,97] and cognitive impairments[42] will intrinsically have less absolute frontal EEG alpha power. To account for these individual differences, calibration and correction algorithms are necessary. Besides a general adjustment according to patient age, cognitive status, etc., preoperative baseline EEG recordings for each patient may be useful. Alternatively, the patient's maximal frontal alpha power could be determined after the patient is in a steady state of unconsciousness before surgical stimulation begins.

Conclusions

EEG reactions to noxious stimuli during general anaesthesia indicate an incomplete blockade of stimulus information entering the central nervous system. Awareness and quantification of these observed EEG reactions might help guide intraoperative clinical decisions by optimising analgesic drug administration separate from anaesthetic titration. The clinician should be aware that nociceptive-induced changes in EEG can be quite variable, and include patterns of *beta arousal*, *delta arousal*, and *alpha dropout*. These EEG changes are often best treated by increased analgesia (opioids, or establishment of regional local anaesthetic blocks) rather than by increased hypnotic drugs. However, at present we have insufficient information to determine if this approach is associated with preferred patient outcomes, and no large randomised trials to test whether nociception-EEG guided manipulation of drug dosage confers widespread beneficial effects.

Authors' contributions

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Writing of the manuscript: PSG, MK, DH, JWS
All authors participated in manuscript revision.

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Decalarations of interest

The authors declare that they have no conflicts of interest.

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